

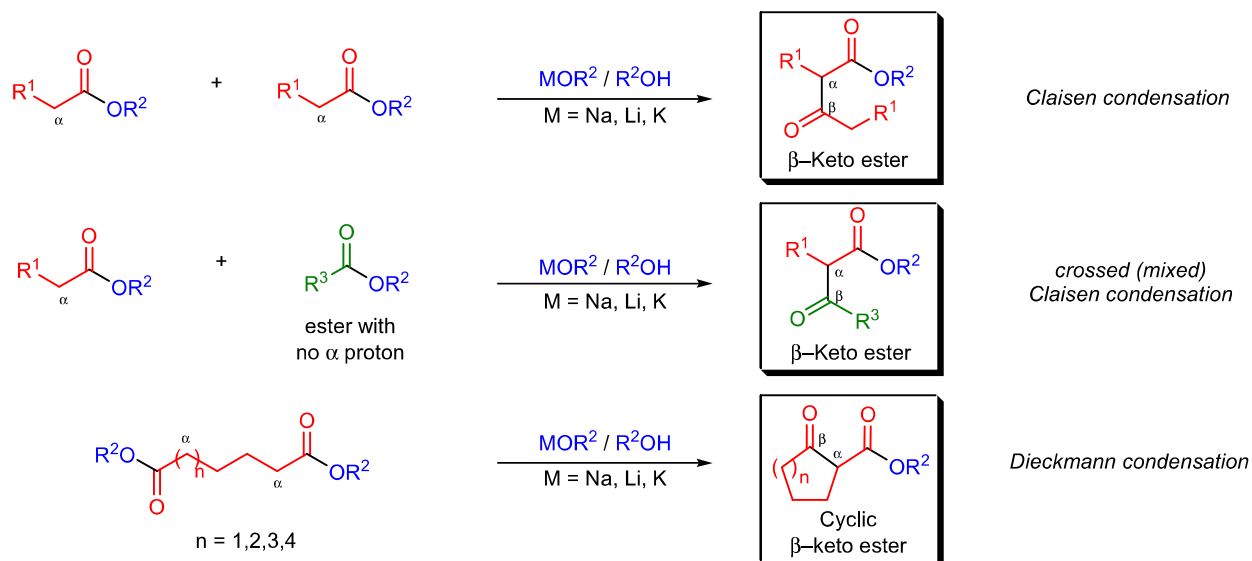
CLAISEN CONDENSATION / CLAISEN REACTION

(References are on page 559)

Importance:

[Seminal Publication¹; Reviews²⁻⁸; Modifications & Improvements⁹⁻¹¹; Theoretical Studies¹²⁻¹⁴]

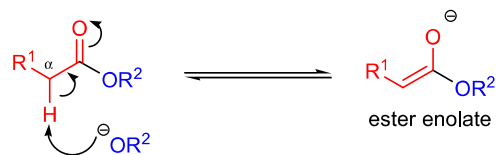
The base mediated condensation of an ester containing an α -hydrogen atom with a molecule of the same ester to give a β -keto ester is known as the *Claisen condensation*. If the two reacting ester functional groups are tethered, then a *Dieckmann condensation* takes place. The reaction between two different esters under the same conditions is called *crossed (mixed) Claisen condensation*. Since the *crossed Claisen condensation* can potentially give rise to at least four different condensation products, it is a general practice to choose one ester with no α -protons (e.g., esters of aromatic acids, formic acid and oxalic acid). The ester with no α -proton reacts exclusively as the acceptor and this way only a single product is formed. A full equivalent of the base (usually an alkoxide, LDA or NaH) is needed and when an alkoxide is used as the base, it must be the same as the alcohol portion of the ester to prevent product mixtures resulting from ester interchange. There are two other variants of this process: a) an ester enolate reacts with a ketone or aldehyde to give a β -hydroxyester, and b) a ketone or aldehyde enolate reacts with an ester to give a 1,3-diketone, both of these are referred to as the *Claisen reaction*. A useful alternative to the *Claisen condensation* is the reaction of an ester enolate with an acid chloride to generate a β -ketoester.



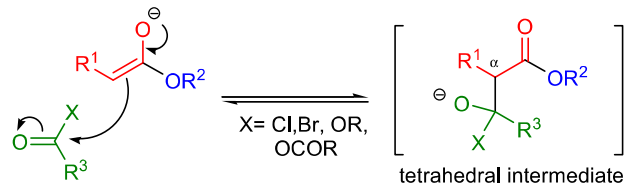
Mechanism: ¹⁵⁻²³

In the first step the base (usually an alkoxide, LDA, or NaH) deprotonates the α -proton of the ester to generate an ester enolate that will serve as the nucleophile in the reaction. Next, the enolate attacks the carbonyl group of the other ester (or acyl halide or anhydride) to form a tetrahedral intermediate, which breaks down in the third step by ejecting a leaving group (alkoxide or halide). Since it is adjacent to two carbonyls, the α -proton in the product β -keto ester is more acidic than in the precursor ester. Under the basic reaction conditions this proton is removed to give rise to a resonance stabilized anion, which is much less reactive than the ester enolate generated in the first step. Therefore, the β -keto ester product does not react further.

First step:



Second step:



Third step:

